

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-331**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

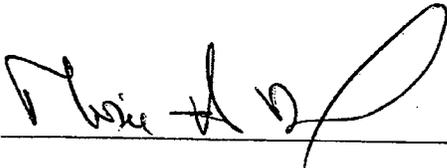
1.2.1.2 Patent Certification

NDA 22-331

Addrenex Pharmaceuticals Inc., is the sponsor of the 505(b)(2) New Drug Application for oral sustained release clonidine hydrochloride 0.1 mg tablets under IND \_\_\_\_\_ The designated indication is for mild to moderate essential hypertension.

b(4)

Addrenex Pharmaceuticals Inc. hereby certifies that, in its opinion; and to the best of its knowledge, there are no unexpired patents for the reference listed drug CATAPRES® Tablets.



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Moise Khayrallah, Ph.D.  
President & CEO

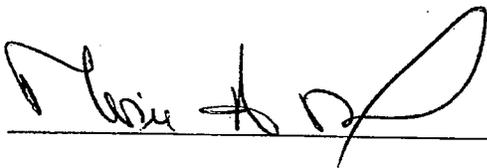
2/13/2008

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Date

**Statement of Exclusivity**

In the opinion of Addrenex Pharmaceuticals Inc., and to the best of its knowledge, in accordance with the list published in the Approved Drug Products with Therapeutic Equivalence, there is no unexpired exclusivity for the reference listed drug, CATAPRES® Tablets.



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Moise Khayrallah, Ph.D.  
President & CEO

2/13/2008

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Date

Department of Health and Human Services  
Food and Drug Administration

Form Approved: OMB No. 0910-0513  
Expiration Date: 7/31/10  
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER  
**22-331**

NAME OF APPLICANT/NDA HOLDER  
Addrenex Pharmaceuticals, Inc.

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)  
Clonibid

ACTIVE INGREDIENT(S)  
Clonidine Hydrochloride

STRENGTH(S)  
0.1mg

DOSAGE FORM  
Sustained-release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 5,869,100	b. Issue Date of Patent February 9, 1999	c. Expiration Date of Patent October 13, 2013
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d. Name of Patent Owner Addrenex Pharmaceuticals, Inc.  Moise A. Khayrallah, Ph.D. President and CEO	Address (of Patent Owner) 4825 Creekstone Drive, Suite 100	
	City/State Durham, NC	
	ZIP Code 27703	FAX Number (if available)
	Telephone Number (919) 941-0800	E-Mail Address (if available) mk@addrenex.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6 Declaration Certification**

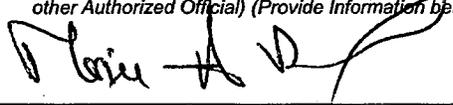
**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed

02/12/2008



**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Addrenex Pharmaceuticals, Inc., Moise A. Khayrallah, Ph.D. President and CEO	
Address 4825 Creekstone Drive, Suite 100	City/State Durham, NC
ZIP Code 27703	Telephone Number (919) 941-0800
FAX Number (if available)	E-Mail Address (if available) mk@addrenex.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 22-331

SUPPL #

HFD #

Trade Name Jenloga

Generic Name clonidine hydrochloride

Applicant Name Addrenex Pharmaceuticals, Inc.

Approval Date, If Known 9/29/09

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17-407                      Catapres Tablets  
NDA# 18-891                      Catapres TTS  
NDA# 20-615                      Duraclon

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES                       NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III      THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The sponsor conducted two trials to support this application:

CLON101- A single-dose PK study comparing Jenloga to Catapres.

CLON201- A 28-day, multi-dose, placebo-dontrrolled study comparing the blood pressure and heart rate effects of Jenloga to placebo.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

CLON101- A single-dose PK study comparing Jenloga to Catapres.

CLON201- A 28-day, multi-dose, placebo-dontrrolled study comparing the blood pressure and heart rate effects of Jenloga to placebo.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 75,614 YES  ! NO   
! Explain:

Investigation #2 !  
IND # 75,614 YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Russell Fortney

Title: Regulatory Project Manager

Date: 9/29/09

Name of Office/Division Director signing form: Norman Stockbridge

Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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*/s/*

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RUSSELL FORTNEY  
09/29/2009

NORMAN L STOCKBRIDGE  
09/29/2009

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-331 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Cardio-Renal PDUFA Goal Date: 9/30/09 Stamp Date: 3/30/2009

Proprietary Name: JENLOGA

Established/Generic Name: clonidine HCl

Dosage Form: Tablet

Applicant/Sponsor: Addrenex Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) Jenloga is indicated in the treatment of hypertension. Jenloga may be employed alone or concomitantly with other antihypertensive agents.

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Jenloga is indicated in the treatment of hypertension. Jenloga may be employed alone or concomitantly with other antihypertensive agents.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	5 yr. 12 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	6 yr. 0 mo.	17 yr. 12 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): 12/31/2011							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22331

GI-1

ADDRENEX  
PHARMACEUTICA  
LS INC

JENLOGA

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/s/

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RUSSELL FORTNEY  
09/29/2009

1.2.1.3 Debarment Certification



www.addrenex.com

1.2.1.3 Debarment Certification

NDA 22-331

Addrenex Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in black ink, appearing to read "Moise A. Khayrallah", is written over a horizontal line.

Moise A. Khayrallah, Ph.D.  
President and CEO

2/13/2008

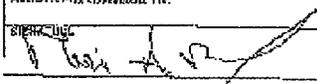
Date

Financial Disclosure: See page 14 of Dr. Williams' Medical review:

3.3 Financial Disclosures

The certificate for financial interest is reproduced below in Figure 1. There is no evidence of conflict of interest by any of the investigators based on this certification.

Figure 1: Financial disclosure certificate

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration		Form Approved OMB No. 0910-0006 Expiration Date: April 30, 2008
<b>CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>		
TO BE COMPLETED BY APPLICANT		
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in accordance with 21 CFR part 312 and that for the purposes of this statement, a clinical investigator includes the sponsor and each dependent child of the investigator as defined in 21 CFR 312.2(f).		
<u>Please mark the appropriate box(es).</u>		
<input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or check list of names to the form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 312.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 312.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other items as defined in 21 CFR 312.2(c).		
<input type="checkbox"/> (2) As the applicant who is submitting a study of new drug sponsored by a firm or body other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (check list of names to this form) did not participate in any financial arrangements with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 312.2(a)) (I had no proprietary interest in the product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 312.2(b))) and was not the recipient of significant payments of other items (as defined in 21 CFR 312.2(c)).		
<input type="checkbox"/> (3) As the applicant who is submitting a study of device sponsored by a firm or body other than the applicant, I certify that I have noted with due diligence to obtain from the listed clinical investigators (check list of names) or from the sponsor the information required under 312.4 and it was not possible to do so. The reason why this information could not be obtained is attached.		
NAME Wase A. Karyem, Ph.D.	TITLE President and CEO	
EMPLOYER/ORGANIZATION Advanis Pharmaceuticals, Inc.		
SIGNATURE 		DATE 07/28/08
Paperwork Reduction Act Statement		
An agency may not conduct or sponsor an information collection and it is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to Washington, DC 20503, and to the Office of Management and Budget, Paperwork Reduction Project (0910-0006).		
FORM FDA 3624 (4/07)		FDA/CDER/Division of Biologics Food and Drug Administration 2025M 003, 0001-0000 Dandridge MD 20727

b(4)

Best Possible Copy

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

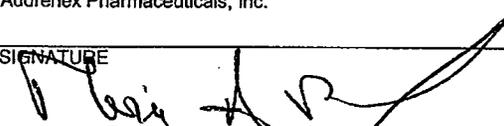
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Moise A. Khayralla, Ph.D.	TITLE President and CEO
FIRM/ORGANIZATION Addrenex Pharmaceuticals, Inc.	
SIGNATURE 	DATE 02/08/2008

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

b(4)

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/s/

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NIKOO N MANOCHEHRI-KALANTARI  
10/08/2009



NDA 22-331

**NDA ACKNOWLEDGMENT**

Addrenex Pharmaceuticals, Inc.  
Attention: Moise A. Khayrallah, Ph.D.  
President & CEO  
4825 Creekstone Drive, Suite 100  
Durham, NC 27703

Dear Dr. Khayrallah:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: CLONIBID (Clonidine HCl Sustained Release Tablets)

Date of Application: February 15, 2008

Date of Receipt: February 19, 2008

Our Reference Number: NDA 22-331

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 18, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review

NDA 22-331  
Page 2

without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Mr. Russell Fortney, R.Ph.  
Regulatory Health Project Manager  
(301) 796-1068

Sincerely,

*{See appended electronic signature page}*

Edward Fromm  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Edward Fromm  
2/26/2008 06:48:57 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-331

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Addrenex Pharmaceuticals, Inc.  
4825 Creekstone Drive, Suite 100  
Durham, North Carolina 27703

Attention: Moise Khayrallah, Ph.D.  
President and CEO

Dear Dr. Khayrallah:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clonidine Hydrochloride Extended-release Tablets 0.1 mg.

We also refer to your May 21, 2009, correspondence, received May 22, 2009, requesting review of your proposed proprietary name, Jenloga. We have completed our review of the proposed proprietary name, Jenloga and have concluded that it is acceptable.

The proposed proprietary name, Jenloga, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 21, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sean Bradley, RPh, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22331	ORIG 1		SYMPRES

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/s/

CAROL A HOLQUIST  
08/14/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 22-331

INFORMATION REQUEST

b(4)

Dear Mr. Smith:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sympres Extended Release Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The MSDS of \_\_\_\_\_ states that a proprietary antistatic agent may be present at \_\_\_\_\_ concentration in \_\_\_\_\_. Declare whether an antistatic agent is present in the \_\_\_\_\_ used for manufacturing of the \_\_\_\_\_. If the antistatic agent is present, provide a CFR citation for food contact of the antistatic agent.

b(4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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RAMESH K SOOD  
08/13/2009



NDA 22-331

INFORMATION REQUEST LETTER

Addrenex Pharmaceutical, Inc.  
Attention: Moise Khayrallah, Ph.D.  
President & CEO  
4825 Creekstone Dr., Suite 100  
Durham, NC 27703

Dear Dr. Khayrallah:

Please refer to your February 19, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for clonidine hydrochloride sustained-release tablets.

We also refer to your submission dated August 28, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

Drug Substance

1. Adopt at least a specific identification test for clonidine hydrochloride and its acceptance criteria after you receive the drug substance from your vendor. Provide the quality of the reference standards that you propose to use for drug substance acceptance.

Drug Product

1. We understand from your pharmaceutical development section and published literature, that the concentration and uniformity of \_\_\_\_\_ control the rate of release of clonidine hydrochloride from the matrix tablet. However, you have adopted compendial specifications for those excipients. Discuss the effect of \_\_\_\_\_ within the USP approved range on the dissolution rate of clonidine hydrochloride and justify those limits via dissolution data. b(4)
2. Similarly, the compendial specification for \_\_\_\_\_ does not include an assay specification for the \_\_\_\_\_. Adopt an assay specification for: \_\_\_\_\_. b(4)
3. Since the particle size of the clonidine hydrochloride is important for content uniformity of the drug throughout the batch, adopt a particle size specification for clonidine hydrochloride with acceptance criteria for D<sub>90</sub>, D<sub>50</sub> and D<sub>10</sub> after manual grinding and screening through \_\_\_\_\_. b(4)

4. Similarly, adopt particle size specification for all excipients, unless justified otherwise.
5. According to your Pharmaceutical Development Report, the uniformity of clonidine hydrochloride, [ ] are critical for the clonidine hydrochloride uniformity and release rate. The content uniformity and release rate are proposed to be tested on limited number of tablets. An assurance of uniformity of clonidine hydrochloride, [ ] throughout the batch is critical for successful manufacture of the batch with consistent quality. Provide a quality risk management plan to assure that the uniformity of the — ingredients could be maintained throughout the batch.
6. Provide the USP<661> and USP<671> information for the container/closure systems or reference appropriate DMFs with date of submission where those information are available. Provide CFR citation for safety of all packaging components or reference appropriate DMFs with the date of submission where those information are available.
7. Adopt microbial limit test such as the one described in the USP <61>. Alternatively, test the drug substance and all excipients for microbial limits as recommended in ICH-Q6A, decision tree #6.
8. Provide CFR citation for the silica gel desiccant bags and provide the DMF reference for necessary CMC information.
9. Since CloniBID tablets contain only — of clonidine hydrochloride, adopt a blend uniformity specification for the final blend to assure that the whole blend is uniform with respect to clonidine hydrochloride. However, you may choose to follow the recommendation of the draft guidance “Guidance for Industry, Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment”.
10. Adopt justified hardness, friability specification for the drug product as recommended in the ICH-Q6A.
11. Complement the identity test by HPLC retention time method with a second identification test with a justified acceptance criteria as recommended in ICH-Q6A.
12. Report all degradation products above 0.1%, as recommended by ICH-Q3B. The degradation products should include each specified and unspecified degradation product, and total degradation products.
13. In your validation report, identify each degradation product via relative retention time of each degradation product found during the forced degradation study. Provide the amount of each degradation product found in the forced degradation study. Provide the mass balance information in the forced degradation experiment. If known degradation products are found, provide the chemical names of those degradants and the quality of the reference standards used to identify them.
14. Provide cross validation data for the data generated using non-validated method, if available.
15. Clarify the dissolution media switch process from pH=2 to pH 7.0; i.e. how the tablet or the media is switched.
16. Provide intermediate precision results of % dissolved from tablets at all time points with different operators, different equipment and different days.
17. Provide individual dissolution values for the clinical trial and primary stability lots.

b(4)

b(4)

18. Provide information on effect of moisture on hardness, friability and dissolution rate.

Label

1. The established name on the container label should read as "CloniBid (clonidine hydrochloride) extended release tablets, 0.1 mg". The established name "clonidine hydrochloride" should have the same prominence as that of the Trademark "CloniBid".
2. Similarly, the established name should be changed in the "Description" section.
3. Provide the carton label.

Drug Master File (DMF)

1. The referenced DMFs are still being reviewed. You will be notified if they are deemed deficient.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Ramesh Sood  
9/23/2008 12:52:15 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-331

**DISCIPLINE REVIEW LETTER**

Addrenex Pharmaceutical, Inc.  
Attention: Moise Khayrallah, Ph.D.  
President & CEO  
4825 Creekstone Dr., Suite 100  
Durham, NC 27703

Dear Dr. Khayrallah:

Please refer to your February 19, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for clonidine hydrochloride sustained-release tablets.

Our review of the Chemistry, Manufacturing and Controls section of your submission is ongoing. In order to complete our review, we request that you provide the following information related to the dissolution specifications:

- The dissolution method development study report
- An explanation of how the method and specifications were chosen
- A detailed report on all other conditions that were investigated (e.g., media apparatus, rotation speed, etc.)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Russell Fortney, Regulatory Health Project Manager, at (301) 796-1068.

Sincerely,

*{See appended electronic signature page}*

Edward Fromm  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Edward Fromm  
8/4/2008 02:46:24 PM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-331 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: CloniBID  
Established Name: Clonidine hydrochloride sustained-release Tablets  
Strengths: 0.1 mg

Applicant: Addrenex Pharmaceuticals, Inc.  
Agent for Applicant (if applicable): N/A

Date of Application: February 15, 2008  
Date of Receipt: February 19, 2008  
Date clock started after UN: N/A  
Date of Filing Meeting: April 11, 2008  
Filing Date: April 19, 2008  
Action Goal Date (optional):

User Fee Goal Date: December 19, 2008

Indication(s) requested: Treatment of hypertension

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 3  
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?  
Datasets provided electronically.

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, 3 Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 75,614

- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) N/A NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 12/6/07 NO   
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 11, 2008

NDA #: 22-331

DRUG NAMES: CloniBID (clonidine hydrochloride) sustained-release tablets

APPLICANT: Addrenex Pharmaceuticals, Inc.

BACKGROUND: The sponsor has developed a sustained release formulation of clonidine tablets. The RLP is Catapres Tablets., approved over 30 years ago. This is a 505(b)(2) application.

ATTENDEES:

Ellis Unger  
Ed Fromm  
Chuck Resnick  
Jim Hung  
Fanhui Kong  
Amit Mitra  
Robert Kumi  
Avi Karkowsky  
Femi Williams

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Williams
Secondary Medical:	N/A
Statistical:	Kong
Pharmacology:	Resnick
Statistical Pharmacology:	N/A
Chemistry:	Mitra
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Kumi
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
OPS:	N/A
Regulatory Project Management:	Fortney
Other Consults:	

Per reviewers, are all parts in English or English translation?  
If no, explain:

YES  NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**  
Any comments: None

**REGULATORY CONCLUSIONS/DEFICIENCIES:**  
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

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Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Catapres Tablets (NDA 17-407)

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

If "Yes," to (c), proceed to question 7.

**NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This new clonidine product is a sustained-release product, while the RLP is an immediate-release formulation.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
  - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):
- NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
  - Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
  - 21 CFR 314.50(i)(1)(ii): No relevant patents.
  - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) Catapres Tablets and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug Clinical and Pharm/Tox*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration



Department of Health and Human Services

Public Health Service

Food and Drug Administration

Rockville, MD 20857

FEB 14 2008

Moise A. Khayrallah, Ph.D.  
President and CEO  
Addrenex Pharmaceuticals, Inc.  
4825 Creekstone Drive, Suite 100  
Durham, NC 27703-8051

**RE: Addrenex Pharmaceuticals, Inc., Small Business Waiver Request 2008.030 for a New Drug Application fee for Clonidine HCl Sustained Release Formulation, NDA 22-331**

Dear Dr. Khayrallah:

This responds to your November 20, 2007, facsimile requesting a waiver of user fees under the small business waiver provision, section 736(d)(1)(D)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2008.030). You request a waiver of the fiscal year (FY) 2008<sup>2</sup> human drug application fee for new drug application (NDA) 22-331, clonidine hydrochloride (clonidine HCl) sustained release formulation. For the reasons described below, the Food and Drug Administration (FDA) grants the Addrenex Pharmaceuticals, Inc. (Addrenex), request for a small business waiver of the application fee for NDA 22-331, clonidine HCl sustained release formulation.

According to your waiver request, Addrenex is a small business with fewer than 500 employees and no affiliates. You also state that Addrenex has no other products of any kind in commercial distribution and that the proposed application, NDA 22-331, for clonidine HCl sustained release formulation based on IND 75,614 will be the first application submitted for Addrenex.

Under section 736(d)(4) of the Act,<sup>3</sup> a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate<sup>4</sup> submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, (2) the business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce, and (3) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

<sup>1</sup> 21 U.S.C. 379h(d)(1)(D).

<sup>2</sup> FY 2008 = October 1, 2007, through September 30, 2008.

<sup>3</sup> 21 U.S.C. 379h(d)(4).

<sup>4</sup> "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).

FDA's decision to grant the Addrenex request for a small business waiver for its NDA for clonidine HCl sustained release formulation based on IND 75,614 is based on the following findings:

- The Small Business Administration (SBA) determined and stated in its letter dated December 11, 2007, that Addrenex is a small business and that it has one affiliate, Alius Pharma, LLC.
- SBA also confirmed that Addrenex and its affiliate have fewer than 500 employees.
- According to FDA records, Addrenex and its affiliate do not have any other drug products that have been approved under human drug applications and introduced or delivered for introduction into interstate commerce. Also, the marketing application for the NDA will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Addrenex or its affiliate.

Consequently, your request for a small business waiver of the application fee for NDA 22-331, clonidine HCl sustained release formulation, is granted provided that FDA receives the marketing application for NDA 22-331 no later than December 11, 2008, 1 year after the effective date of the size determination made by SBA.

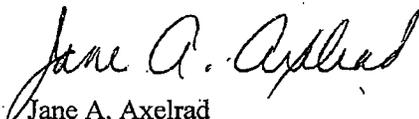
We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for Addrenex's NDA 22-331, clonidine HCl sustained release formulation based on IND 75,614. FDA records show that Addrenex has not yet submitted the NDA in full.

Once the full application is received, if FDA refuses to file the application or if Addrenex withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Addrenex should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG  
USER FEE COVER SHEET**

Form Approved: OMB No. 0910-0297  
Expiration Date: December 31, 2006.

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<b>1. APPLICANT'S NAME AND ADDRESS</b> Addrenex Pharmaceuticals, Inc. 4825 Creekstone Drive, Suite 100 Durham, NC 27703-8051		<b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b> NDA 22-331				
<b>2. TELEPHONE NUMBER (Include Area Code)</b>  ( 919 ) 941-0800		<b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).				
<b>3. PRODUCT NAME</b> CloniBID (Clonidine HCl Sustained-Release) Tablets		<b>6. USER FEE I.D. NUMBER</b>				
<b>7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</b>  <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)  <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)  <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)  <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)						
<b>8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <i>(See item 8, reverse side if answered YES)</i>						
<p><b>Public reporting burden for this collection of information</b> is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table><tr><td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td><td>and</td><td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td><td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td></tr></table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
<b>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</b> 	<b>TITLE</b> President and CEO	<b>DATE</b> 02/14/2008				

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX  
10903 NEW HAMPSHIRE AVE  
BLDG. 22  
SILVER SPRING, MD 20993



***US Mail address:***

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

**Attention:** Dr. Moise A. Khayrallah

**Sponsor:** Addrenex Pharmaceuticals, Inc.

**Phone:** (919) 941-0800

**Subject:** IND 75, 614  
Preliminary Response

**Date:** January 22, 2008

**Pages including this sheet:** 9

**From:** CDR Denise M. Hinton

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**IND 75, 614**  
**Addrenex Pharmaceuticals, Inc.**  
**Type B Pre-NDA Meeting**  
**Meeting Minutes**

Meeting Date: December 6, 2007  
Application: IND 75, 614  
Drug Name: Clonixel (clonidine HCl sustained release) Tablets  
Type of Meeting: Type B Pre-NDA

Meeting Chair: Norman Stockbridge, M.D., Ph.D.  
Meeting Recorder: Denise Hinton

**Division of Cardiovascular and Renal Products**

Norman Stockbridge, M.D., Ph.D.	Division Director
Akinwale Williams, M.D.	Clinical Reviewer
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology
Robert Kumi, Ph.D.	Clinical Pharmacologist
Denise Hinton	Project Management Staff

**Addrenex Pharmaceuticals, Inc.**

Moise Khayrallah, Ph.D.	President and CEO
Sanjay S. Patel, Ph.D.	Vice President, Scientific Affairs
Paul Ketteridge, RPh	Regulatory Affairs Consultant
	Pharmacokinetics Consultant
David Ward, M.D.	Medical Consultant

**b(4)**

**Background:**

Clonixel is a patented oral dose, sustained release formulation of clonidine hydrochloride USP, a mesomeric imidazoline derivative indicated for the treatment of hypertension. Clonixel may be employed alone or concomitantly with other antihypertensive agents.

The Sponsor requested this meeting to discuss the submission of an NDA for Clonixel on the basis of pivotal data from two clinical studies and to discuss the consideration for granting a full waiver of the requirement to submit the pediatric assessments specified in PREA for Clonixel. The Division previously met with the sponsor on November 1, 2006 and July 13, 2007.

**Questions, Discussion, and Agreements:**

After introduction of attendees, the Sponsor, Addrenex, presented slides to address each of the FDA preliminary responses.

**FDA Preliminary Response:**

1. Does the Division agree that the pharmacokinetic and pharmacodynamic data presented in this package are adequate, if confirmed in the final analysis, to proceed to submission of an NDA under (505) (b) (2) regulations?

**FDA response:** No, you have not provided sufficient evidence to demonstrate safety and efficacy of your proposed formulation.

The development of a new sustained release formulation of an available immediate release formulation necessitates that you adequately determine those aspects for which you cannot rely on the immediate release formulation. In this case, you would need to demonstrate that the effect of your clonidine formulation affords blood pressure effect for the entire dosing interval. In the information you submitted we only have 24-hour average effects. We would also need to see if the effect of your formulation affords adequate blood pressure response at nadir of concentrations. To assess nadir effect we suggest that you perform an analysis of the last 2 hours of the interdosing intervals of the ambulatory data. Since there was no concurrent placebo group, you would of necessity have to rely on changes from baseline measurements.

We also note that you do not have any data on blood pressure effects with a once-daily dosing regimen. Based on the kinetic profiles you submitted, it is possible that a once-daily dosing regimen may be feasible. We encourage the assessment of a once-daily regimen in a clinical study.

We do not have adequate information on how the ambulatory blood pressure measurements were collected in study CLON-201. If the ABPM, which served as a qualification measurement, also provide the assessment of the baseline effect, the baseline measurement would likely be an overestimate of the patient's true blood pressures (regression to the mean effect). Subtraction of the measured effect at the interdosing interval would give an overestimate of the drug effect.

We also do not have an adequate reason why the drug dose studied was limited to the 0.6 mg dose. For a new sustained release formulation, anticipating that lack of or degree of tolerability may be limited by  $C_{max}$ , we generally ask that the dose range be extended, to where there is either a plateau in the effect of drug or until intolerable adverse events become common. Your development program is inadequate to conclude that the whole useful dosing range has been explored. The current Catapres labeling indicates that the potential therapeutic dosage range extends to as high as 2.4 mg. Assuming that your proposed formulation has similar bioavailability to Catapres, it is likely that a much larger dose range of your formulation should be explored.

The mean data you have generated to date suggest that your proposed clonidine formulation delivers the drug in a fairly sustained manner, relative to the immediate release product. However, your PK/PD data do not evaluate dose-exposure (proportionality) over the anticipated therapeutic dose range.

You can address the preceding concerns by providing or generating the following information:

- comparative data showing that your proposed formulation has a similar PK/PD relationship as approved clonidine product(s) and
- comparative data showing that the exposure produced by your formulation brackets that of approved clonidine formulations over the anticipated therapeutic exposure range, if the input function does not affect response.

Additional Comments:

- In your PK/PD modeling you should consider the time-course of the effect, by evaluating plasma concentration and blood pressure data simultaneously as a function of time.
- Please note that mean 24-hour blood pressure measurements are not considered appropriate for PK/PD analysis.

**Discussion during the meeting:**

**b(4)**

The Sponsor intends to file this NDA with the current formulation, which delivers steady plasma concentrations and steady blood pressure control throughout the b.i.d. dosing interval. The Sponsor also has future plans to study \_\_\_\_\_; however, the current data only support a b.i.d dosing regimen.

**b(4)**

**Regression to the Mean Effect**

There was a brief discussion about regression to the mean effect. The Sponsor acknowledged that regression to the mean may complicate the analysis of antihypertensive effects of study medication when qualifying ABPM also provides data for assessment of Baseline BP, in the absence of a placebo control, and when baseline assessment of hypertension is based on limited data.

As shown on their slides and in discussion, the sponsor confirmed that in CLON-201, the entry criteria were based on ABPM from 12 time points during 12-hour period. They explained that prior to baseline ABPM, patients had office sitting systolic blood pressure (SSBP) and sitting diastolic blood pressure (SDBP) taken at Screening and Days -14, -7, and -1:

- 36 of 40 (90%) had most assessments of SSBP  $\geq 140$  mmHg and the same percentage had SDBP  $\geq 90$  mmHg

- On Day -1, 39 of 40 (98%) had SSBP  $\geq$ 140 mmHg OR SDBP  $\geq$ 90 mmHg and 34 of 40 (85%) had both pressures above these ranges.

**Rationale for Dose Range of 0.2 – 0.6 mg/Day**

The sponsor supported their case for the proposed dose range by referring to literature. They stated that authors in both the Wing et al. and Davies et al. papers speculated that stimulation of peripheral post-synaptic alpha adrenoceptors by high plasma concentrations of clonidine accounted for the attenuation of BP lowering effects.

**From the FDA review of NDA 18-891 (Catapres TTS)**

By the time the Catapres TTS patch was approved, FDA recognized in the labeling that “An increase in dosage above two Catapres-TTS-3 [i.e. 0.6 mg/day] is usually not associated with additional efficacy”.

The maximum dose of CatapresTTS presented to FDA for review of the NDA was approximately 12 cm<sup>2</sup> (3 x 3.9 cm<sup>2</sup>). This corresponds to approximately 0.34 mg/day of oral clonidine.

The sponsor concluded that exposing patients to doses > 0.6 mg/day was unlikely to yield clinical benefits and may expose subjects to unnecessary risk.

The Division stated that the Sponsor’s approach is reasonable. If 2.2 µg/mL is the highest concentration of the therapeutic concentration window generated by other approved formulations. The Sponsor needs to ensure that the concentration achieved by the proposed formulation achieves the highest concentration in that window. Dr. Marroum also stated it would be important for the Sponsor to demonstrate that the dose remains in the therapeutic range in the 3 studies. The dose should be titrated and to give concentrations within the therapeutic window throughout the dosing interval.

The Sponsor agreed with Dr. Marroum’s response with regard to the therapeutic window. They will describe the process used in the NDA submission.

FDA Preliminary Response:

2. Does the Division agree that a full waiver of the pediatric requirements is warranted for this application?

**FDA response:** No. The rationale you gave for not performing pediatric studies is inadequate. As far as we can tell there is no available information that clonidine is either useless or harmful in pediatric populations. Consequently, we cannot grant a waiver from PREA responsibilities.

**Discussion during the meeting:**

The Sponsor referred to the FDC Act-505B(a)(4)(A)(ii) which states “(A) FULL WAIVER- On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection if the applicant certifies and the Secretary finds that--

- (i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);
- (ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or
- (iii) the drug or biological product—

**(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and  
(II) is not likely to be used in a substantial number of pediatric patients.”**

The Sponsor stated that the statement above is different from the Division’s statement that there is no evidence that the product is useless. If the product is useful, but there is no meaningful benefit over existing treatments, and is unlikely to be used in substantial numbers, their request for a waiver meets the statute requirements above.

The Sponsor stated that there is evidence strongly suggesting that clonidine may be unsafe when used for hypertension in the pediatric population and referred to the approved label of Catapres tablets to support their request for a full waiver. The Catapres label states:

**Warnings Section-“Because children commonly have gastrointestinal illnesses that lead to vomiting, they may be particularly susceptible to hypertensive episodes resulting from abrupt inability to take medication.”**

The sponsor concluded the following:

- Clonidine’s safety in pediatric populations is a concern (Catapres label)
- Other classes (diuretics, ACE, CCB, B-blockers, ARB) are recommended in pediatric hypertension literature
- Safety concerns with clonidine and availability of multiple other recommended regimens
- Clonidine will not represent a meaningful therapeutic benefit over existing therapies
- Based on literature recommendations, clonidine unlikely to be used by a substantial number of pediatric patients

Dr. Stockbridge considered the Sponsor’s response, and observed that while the literature search showed that the drug product has not been used, it did not show that

it has actually been studied and it is futile to use in pediatrics. The sponsor needs to convince us that the rebound is a phenomenon in adults and children.

The data will need to show that children cannot tolerate the drug and this phenomenon poses a safety issue. The Sponsor was advised to assess whether children are prone to discontinue use of the drug because of gastrointestinal issues or hyperemesis, leading to rebound hypertension as a consequence of the missing doses. After providing the recommended data, the Sponsor is invited to present the information to the Division to decide if it is worth studying in the pediatric population. The Sponsor's position as presented in the briefing package will not release the sponsor from PREA obligations.

The Sponsor will consider the Division's recommendations and discuss it with us again at a later date.

FDA Preliminary Response:

3. Is the proposed content and format of the NDA acceptable to the Division?

**FDA response:** The content of the NDA will be a review issue upon submission of the NDA. The format proposed for Modules 1 through 4 is acceptable. Modifications to include safety and efficacy data for any additional studies are required for Module 5 and a statistical analysis plan should also be added for additional clinical studies.

Discussion during the meeting:

The proposed content and format of the NDA are acceptable to the Division.

Meeting recorder: \_\_\_\_\_  
Denise M. Hinton

Meeting concurrence: \_\_\_\_\_  
Norman Stockbridge, M.D., Ph.D.

Draft: 20Dec07  
Final: 22Jan08

RD:  
Kumi 01/15/08  
Marroum 1/17/08  
Williams 1/21/08  
Karkowsky 1/22/08  
Stockbridge 1/22/08

Linked Applications

Sponsor Name

Drug Name

IND 75614

ADDRENEX  
PHARMACEUTICALS

CLONICEL(CLONIDINE HCl SUSTAINED  
RELEASE

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

DENISE M HINTON  
01/22/2008

NORMAN L STOCKBRIDGE  
01/22/2008

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-331 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Jenloga Established/Proper Name: clonidine hydrochloride Dosage Form: Tablet		Applicant: Adrenex Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Russell Fortney		Division: Division of Cardiovascular and Renal Products
<p><b>NDAs:</b>            NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)            Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 17-704 Catapres</p> <p>Provide a brief explanation of how this product is different from the listed drug.            Jenloga is a "modified-release" formulation of clonidine with different release and absorption characteristics compared to Catapres tablets.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input checked="" type="checkbox"/> No changes      <input type="checkbox"/> Updated            Date of check: 9/29/09</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		9/30/09 9/29/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None    CR, 12/19/08

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials (*accelerated approvals only*)

Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf>). If not submitted, explain \_\_\_\_\_

Received

**Appears This Way  
On Original**

❖ Application Characteristics <sup>2</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	9/23/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<b>Included</b>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<input checked="" type="checkbox"/> Included
<p>Documentation of consent/non-consent by officers/employees</p>	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) CR; 12/19/08 AP 9/29/09</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	9/29/09
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	8/15/08
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	Catapres label
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide  <input type="checkbox"/> Patient Package Insert  <input type="checkbox"/> Instructions for Use  <input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels (full color carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	9/29/09
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	8/13/09 8/14/09
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 8/28/09, 9/18/09 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> SEALD 9/25/09
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	Filing review 4/11/08; RPM Application Overview 9/28/09
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable 9/23/09
<ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>• Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 1/22/08
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
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<ul style="list-style-type: none"> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/28/09, 12/19/08
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/16/08
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	9/22/08
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	see 9/22/08 medical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	see 9/22/08 medical review
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 12/17/08, 11/7/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/29/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 9/25/09
• Product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 9/29/09, 9/25/09, 12/19/09, 12/17/09, 11/12/08, 3/10/08
• ONDQA Biopharmaceutics review (indicate date for each review)	9/28/09, 9/3/09, 12/15/08
• BLAs only: Facility information review(s) (indicate dates)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	see 11/12/08 CMC review
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: 6/4/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>○ TBP-EER</li>   <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li> </ul> </li> </ul>	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p> <p>Date completed:</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Accepted   <input type="checkbox"/> Hold</p>
<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Not yet requested</p> <p><input checked="" type="checkbox"/> Not needed</p>

### Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.